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Exercise Improved Age-associated Changes in the Carotid Blood Velocity Waveforms

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Abstract

Physiological blood flow velocity in common carotid artery (CCA) is altered markedly with advancing age. It is unknown that regular aerobic exercise is able to improve blood flow velocity waveforms in either healthy young or healthy older individuals. We investigate the role of regular exercise on the age-associated alterations in blood velocity waveforms in CCA by using cross-sectional and intervention approaches. First, we study 91 putatively healthy volunteers with age range of 20-76 years: 65 subjects are sedentary and 26 subjects are regular exercise-trained. We assess the blood velocities at rest in peak systolic (S1), second systolic (S2), incisura between systole (I) and peak diastolic (D), and end-diastolic (d) in young, middle-aged and older subjects. Blood velocities in S1 are higher in exercise-trained, whereas S2, D and d are not different between trained and sedentary individuals. However, the indices of S1/S2 and D/I have marked higher values in exercise-trained adults. Second, we study 7 young sedentary healthy subjects before and after 1-month aerobic exercise intervention. The aerobic exercise increases whole velocity waveforms in CCA with association of decreased heart rate. In conclusion, regular exercise improves age-associated decrease in blood flow velocities in the healthy young, middle-aged and older individuals and restores levels after 1-month exercise in previously sedentary young men.

Keywords: Doppler ultrasound, portable telemetry system, blood velocity waveform, age, aerobic exercise training

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1 INTRODUCTION

The age-associated alterations in the cardiovascular response to exercise training are evident. The hallmarks of cardiovascular aging are decreased for maximum heart rate, ejection fraction, maximal oxygen intake, maximal cardiac output and artery compliance [1, 2].

The age-associated decline in flow velocities in CCA is known [4-6, 22-25]. Most of the studies focused on blood flow in S1 and d velocities, and demonstrated that the velocities decrease with age [4-6, 22-25]. Although, physiological blood flow velocities in common carotid artery (CCA) change markedly with advancing age, but it is unknown that aerobic exercise training can alter and improve blood flow velocity waveforms in either healthy young or healthy older individuals.

A fundamental understanding of age-associated changes in cardiovascular circulation and function is required for effective and efficient prevention and treatment of cardiovascular disease in older persons [1]. For investigating the haemodynamics of cerebrovascular and cardiovascular circulation, Doppler ultrasound is a popular technique. Doppler ultrasound was used firstly by Satomura about 50 years ago [3] and has dramatically evolved in the last decade.

Numerous studies have presented that spectral analysis of Doppler signal and blood flow waveforms in CCA changes with aging and with vascular disease.

These analyses are extremely powerful noninvasive tool for clinical diagnosis such as in the carotid artery disease [4-9].

Despite accumulations of the evidence for the age-associated decrease in cardiovascular function, the extent to which the habitual exercise training can improve blood flow velocity waveforms of CCA in the human is not well documented. Accordingly, the aim of the study is to investigate that the regular aerobic exercise training can improve the age-associated decreases in blood flow velocity waveforms in CCA. To comprehensively address this aim, we use two different approaches: Protocol 1 (cross-sectional study) is designed to investigate the potential benefit of regular physical activity in the primary prevention of age-associated decreases in blood velocity waveforms.
Protocol 2 (intervention study) is designed to investigate whether regular aerobic exercise training could enhance blood velocity waveforms in young sedentary subjects.

In the previous studies, we have presented that our telemetry system has enough performance to get accurate data for estimation of blood circulation during exercise in both aerial and aquatic environments [10-14]. For the present study, we improve the portable velocimeter system and develop real-time signal processor with stand-alone application. Using the system, the blood flow velocities in CCA in 114 healthy volunteers with age range of 20-76 years are analyzed quantitatively.

2 METHODS AND MATERIALS

2.1 Subjects and experimental protocol

We examined a total of 105 healthy subjects. For protocol 1, we studied the selected 91 putatively asymptomatic healthy volunteers with ages 20-76 years (65 subjects were sedentary and 26 subjects were exercise-trained). There were 3 classified groups from 20-years-old to 76-years-old in 19-year-old intervals: 1st group was the young group (n= 27, age range: 20-38), 2nd was the middle group (n= 39, age range: 39-57), and 3rd was the older group (n= 23, age range: 58-76). In the study, exercise-trained subjects were chosen due to their regularly performed aerobic physical exercise training (an average of 3 times/week and 1 hour/times). Estimation of physical activity level in the group populations were assessed using our standardized questionnaires and resting heart rate level. For protocol 2, 14 healthy young subjects participated in a 1-month aerobic exercise intervention programme (primary running of 3 km in the road). They were requested to make no changes to their diet, therapy, or other daily routine for the duration of the study. They were medically examined before the start of the study to ensure their capability of participating in the training. All the selected subjects were normotensive, and free of overt chronic diseases as assessed by medical history.

All subjects gave their written informed consent to participate. This study was reviewed and approved by the Ethics Committee of Tokushima University Hospital.

2.2 Telemetry measurement system

We developed a portable device for measuring blood velocity using Doppler ultrasound in CCA with synchronized measurement of ECG [15, 16]. The system consisted of an ultrasound probe, a main unit, a receiver module, an analog-digital (A/D) converter board and a laptop personal computer (PC) as shown in Fig. 1. The main unit consisted of a Doppler signal discriminator (DSD), a transmitter (F01ATX) and a 9V battery.

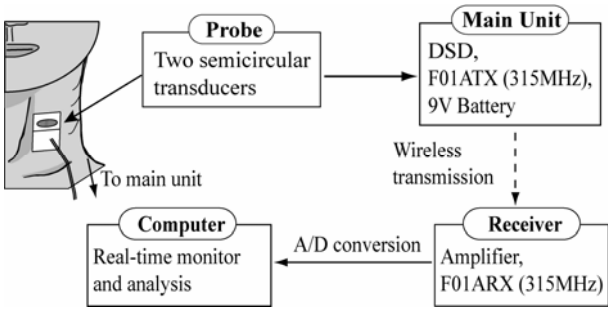

Figure 1: Portable measurement system of blood flow velocity with real-time monitoring.

As in the previous studies, we managed to telemeter blood flow velocity in carotid and brachial artery with synchronized electrocardiogram (ECG) in good enough performance during an exercising man [10, 13, 15, 16]. However the telemeter system was unsuitable for use as a portable device due to the larger size.

In the present study, the system was improved by miniaturizing the DSD, upgrading the probe with good attachment on the skin and developing the stand-alone real-time software package for measurement of blood flow velocity spectra with synchronized monitor of electrocardiogram (ECG), and blood pressure (BP). The DSD was miniaturized using mount-surface technique, and the downsized substrate size was 67×48 mm. It provided more performance for monitoring blood flow velocity during physical exercises and postural changes, due to the miniaturization of the DSD. The power consumption of the main unit was reduced to 2.1 W, therefore it enabled the battery installed in the portable system to be used more for than 10 hours.

Commercially available Doppler probes were unsuitable and expensive for portable use. Therefore, we constructed the purpose-built probes with two semicircular piezoelectric transducers (PZT) with a diameter of 15 mm, where one was for transmitting ultrasound and the other was for receiving the echoes using continuous-wave (CW) ultrasound [15-17]. The probe was designed with a small size (W34×H20×D42 mm^3, approximately weighing 20 g). A transmitter transducer chosen for clinical use had an intensity output of 8 mW/cm^2 spatial peak-temporal average (SPTA) as measured by a 0.4 mm diameter needle hydrophone (ONDA, model HNV-0400). The ultrasonic output intensity was safe for the human tissue

as approved by U.S. Food and Drug Administration (FDA).

In this study, the ultrasonic probe was attached to the left side of neck with an insonation Doppler angle of 50 degrees which was fixed with a band and wound around the neck. An accurate estimation of spectral velocity was dependent on the insonation of beam whereas the insonating angle was not a sensitive function if CCA was hypothesized to be parallel to the skin. An exact attachment position in measuring blood flow velocity in CCA was between the sternocleidomastoid muscle and the throat at a level between the fourth and fifth cervical vertebrae.

2.3 Real-time processing monitor

In the real-time processing monitor implementation, two main specifications had been taken into account. First, the execution time of signal processing must be low to avoid overloading the available system resources. Second, the output latency time was kept as short as possible (less than 100 ms) to synchronize the sound with another output display (corresponding real-time spectrogram).

The signal processing had been implemented through a program written in Visual C++ ® for a stand-alone Windows ® application. The real-time spectrogram monitor was implemented using the loop timer method. Timer was set as 50ms corresponding to the sampling data of 500 points. However, data were analyzed using fast Fourier transform (FFT) with multiples of 256 points of Hanning window. The spectrogram was processed using decimation in frequency (DIF) radix-2 FFT algorithm, which had smaller discrete Fourier transform (DFT) computations in order to reduce the computation time. To increase the efficiency, decomposed DFT was optimized by processing the real signal which was called real-only FFT computation.

The software used two circular buffers to store the samples at the input and output for stream data path respectively. The samples coming from an acquisition system were stored at a sampling frequency (fs) in the working buffer as sources for the signal processing. The processed signal was then stored in the rendering buffer, where it was available for rendering in the spectrogram. The acquisition system from A/D conversion was linked through dynamic-link library (DLL) to signal processing program.

As reported in Table 1, the average of CPU load, memory utilization, and computation time were measured in 2 laptop PCs of different performance. Results show that the full operating software yielded CPU load lower than 5 on a recent laptop PCs, and the value about 25% for a quite obsolete laptop PC. Due to the usage of set timer method, output latency was depended on timer rate, 50 ms. If signal processing time was less than set timer rate, latency time was constantly maintained. The computation time was lower than 1ms when tested in the recent laptop PC. However, the computation time was larger, about 16ms in the quite obsolete laptop PC, so that latency time for rendering spectrogram was still maintained at rate of 50 ms.

Table 1: The Performances in CPU load, memory utilization and computation time

	CPU load (%)	Memory utilization (kB)	Computation time (ms)
Pentium® M 1.60 GHz, 512 MB RAM	3	5756	< 1
Pentium® 3 1.0 GHz, 256 MB RAM	25	5304	16.2

2.4 Data measurements

Blood flow velocities were measured from the Doppler shift of received signals in CCA. The signals which included a low-frequency noise and a harmonics noise were filtered by band-pass filter of 0.1 to 4.2 kHz in the DSD. From that range of the frequency, blood flow velocities could be taken out. The velocity (V_d) could be estimated from its Doppler shift frequency (f_d) as $V_d=cf_d/(2f_0\cos\theta)$ where, c=1540 m/s, the speed acoustic wave in human tissue; f_0=2.0 MHz, an irradiated ultrasound frequency and θ=50 degrees, the Doppler angle of insonating.

In the study, the data were acquired at 10 kHz of fs through a 16 bit-A/D converter (Interface, CBI-360116TR, Japan). It was repeatedly analyzed by using FFT with successive 25.6 ms, which were given by shifting 12.8 ms in turn. Therefore, an instantaneous spatial spectral frequency was calculated at 12.8 ms intervals with 39 Hz per point of frequency resolution.

Blood flow velocity spectra were measured in the relaxed sitting posture (1 minute for cross-sectional and 3 minutes for intervention studies). Data collections were performed with synchronized monitoring of ECG and BP using a developed real-time processing monitor. We used commercially available device for ECG (MEG 2100, Nihon Kohden, Japan) and for BP (Tango, SunTech Medical, USA) to measure heart rate (HR) and left upper arm BP, respectively.

2.5 Characteristic velocity waveforms

A threshold method was implemented to extract instantaneous peak-velocity (V_p) values from the spatial velocity spectra. The velocity waveforms were computed using ensemble average of Vp envelope. We selected 30 consecutive cardiac cycles of those to characterize the feature points as illustrated in Fig. 2.

Characterization of the feature points were given as below; S1: the first peak systolic velocity wave (maximum velocity), S2: the second systolic velocity wave, I: incisura between systole and diastole, D: the peak diastolic velocity wave, and d: the end-diastolic minimum velocity [18, 19]. Peak velocity S1 represent the highest velocity achieved during systole. It was commonly used as an ejection parameter for cardiac systole. An augmented S2 in late systole was related to the reflection of pulse wave velocity that rises at branching point, area of alterations in elastance and high-resistance arterioles. D velocity wave was the peak

diastolic velocity, which rise due to vascular elastic recoil at maximum rate during the cardiac diastole.

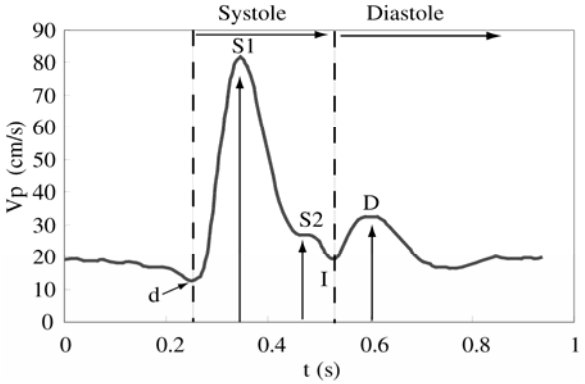

Figure 2: Characteristic features on waveform: Ensemble-average velocities of 30 consecutive cardiac cycles in a young subject. S1: the first peak systolic velocity wave (peak velocity), S2: the second systolic velocity wave, I: incisura between systole and diastole, D: the peak diastolic velocity wave, and d: the end-diastolic minimum velocity.

From these, blood flow velocity indices of S1/S2, d/S1, D/I and RI (resistance index) were calculated. The indices were dimension-less and independent of the angle insonation. Gosling et al. was first used S1/S2 (as called A/B ratio) in CCA and superorbital arteries for detecting occlusive disease in the internal carotid artery (ICA).

The parameter of d/S1 as an index of blood flow in CCA was used by Yuhi to assess cerebrovascular disease [6]. Nagamoto et al. also used the index and classified the velocity waveforms by measuring the blood flow in the CCA of elderly nursing home residents [4].

Resistance index was used as a typical peripheral vascular resistance index that could be calculated from waveforms as (S1-d)/S1, where the smaller the value of RI, the lower its resistance and vice versa. The index was first used by Pourcelot on flow velocity waveform in CCA [20, 21].

The ratio of D/I may be provided to evaluate the magnitude of vascular elastic recoil during cardiac diastole that was exerted by its smooth muscle cells. The ability of an artery to recoil with cardiac pulsation reflects to vasoconstrictor, which was typically governed by the need to control systemic vascular resistance, venous pooling, and intravascular blood volume.

2.6 Statistical analysis

Normal distribution of data was verified by Kolmogorov-Smirnov goodness-of-fit test. A two-way analysis of variance (ANOVA) was used to determine the effect of exercise and aging in the results of protocol 1. Three designed age-groups of significant pairwise differences were determined using Tukey's post-hoc test. The effects of exercise training were compared by ANOVA, which provided two *p* values. The first *p* value represent the effects of exercise training on the entire group, combining the young, middle-aged and older subjects as a single group. The second *p* value represent the interaction of exercise training and age-groups (exercise training effect * 3 age-groups). This statistic indicated any differential training effects in the young, middle-aged and old subjects. For protocol 2, training effect was determined using *t*-test. The relationships between all variables and age were determined using the Pearson's correlation. All data were reported as means and standard error (SE). The significance level was set at 0.05.

3 RESULTS

3.1 Protocol 1

Table 2: Selected subject characteristics of cross-sectional study

Variable	Sedentary			Exercise-trained		
	Young	Middle	Older	Young	Middle	Older
n	17	29	19	10	11	5
Age (years)	28 ±1	51±1*	68±1*†	28±2	54±1*	64±1*†
Height (cm)	162±4	169±5	160±1	165±2	166±2	168±1§
Weight (kg)	54±5	71±7*	60±3	58±3	69±1*	64±1
BMI (kg/m^2)	21±1	25±1*	23±1	21±1	25±1*	23±0.3
Systolic BP (mmHg)	115±4	129±4	131±7*	119±4	128±3	132±4*
Diastolic BP (mmHg)	72±3	80±3	82±6	73±4	83±3	87±4
Pulse BP (mmHg)	43±2	49±4	49±1*	46±3	45±1	65±7*
Heart rate (bpm)	76±3	79±1	73±3	66±4§	65±3§	68±5

All data are mean ± SE; *n*, no. of subject. *p<0.05 versus young; †p<0.005 versus middle-aged; ‡p<0.05 versus older; §p<0.05 versus sedentary of same age group. Legend: body mass index (BMI), millimeter of mercury (mmHg), beats per minutes (bpm).

Table 2 shows the selected subject characteristics for the cross-sectional study. The subjects exercised regularly on an average of 3 times per week for 1 hour each time. Prior to this, they had regular physical training for more than 6 months. The exercise training included tennis, walking and jogging.

There were no significant group difference in height, heart rate and diastolic blood pressure. Weight and body mass index (BMI) were significant larger in the middle-aged group. Systolic and pulse blood pressure were significantly higher in older sedentary and exercise-trained group. The exercise-trained in young and middle-aged had significant lower heart rate during resting.

The results of cross-sectional study were presented in three sections: as the overall and pairwise differences between the young, middle-aged and older groups, as the effects of exercise training with both young, middle-aged, and older groups combined as a single group, and differential effects of exercise training in the three-group design.

3.1.1 Age-associated changes in flow velocity waveforms

Table 3 show the overall and pairwise comparisons of blood flow velocity waveforms and its parameters of blood flow in young, middle-aged, older groups. Blood flow velocities in S1, D and d were significantly different in the three groups by ANOVA (p<0.05). The dimensionless waveform indices of d/S1, S1/S2, D/I and RI also had significance on the entire group. The significance in HR was not found in the designed three age-groups.

Table 3: Age-associated changes in flow velocity waveforms

Variable	Young	Middle	Older	P
d (cm/s)	23±1	22±1	18±1*†	0.043
S1 (cm/s)	104±3	82±4*	76±4*	<0.0001
S2 (cm/s)	54±3	60±3	57±3	0.37
I (cm/s)	29±2	33±2	28±2	0.18
D (cm/s)	42±2	39±2*	32±2*†	0.006
d/S1	0.21±0.01	0.29±0.01*	0.24±0.01†	<0.0001
S1/S2	2.01±0.07	1.38±0.07*	1.36±0.07*	<0.0001
D/I	1.48±0.03	1.20±0.04*	1.18±0.04*	<0.0001
RI	0.79±0.01	0.71±0.01*	0.76±0.01†	<0.0001
HR(bpm)	72±2	71±2	71±2	0.83

Data are means ± SE. Tukey significances *p<0.05 versus young and †p<0.05 versus middle. Data are included exercise-trained and sedentary subjects in the young, middle-aged and older groups.

From post-hoc analysis, S1 and D velocities were significantly lower in the middle and older age-groups (p<0.05). They were significantly lower in the middle and older age-groups for D velocities. The velocities of d were significantly lower in the older age group (p<0.05 versus young and middle age-groups). Otherwise, there were no significant differences in I and S2 velocities between the three age-groups. Consequently, the indices of S1/S2 and D/I were significantly lower in the middle and older group (p <0.0001). The d/S1 index increased significantly in the middle-aged group (p<0.05) and decreased significantly in the older group (p<0.05). Inversely, RI decreased in the middle-aged and increased in the older groups (p=0.005). There was no significant change in HR between three age-groups.

3.1.2 Effects of exercise on the entire groups

Table 4 show the effect of exercise training (p by ANOVA) on flow velocities and its indices. The results

Table 4: Effect of exercise on flow velocity waveforms

Variable	Sedentary	Exercise	p by ANOVA	
			Training effect	Training *young/ middle/ older
d (cm/s)				
Young	25±1	19±2	0.26	NS
Middle	23±1	22±2		
Older	17±1	21±2		
S1 (cm/s)				
Young	99±4	109±5	0.001	NS
Middle	75±4	97±6		
Older	69±4	91±7		
S2 (cm/s)				
Young	56±4	53±5	0.94	NS
Middle	60±3	60±5		
Older	56±4	58±6		
I (cm/s)				
Young	31±2	27±3	0.83	NS
Middle	33±2	33±3		
Older	27±2	30±3		
D (cm/s)				
Young	42±2	42±3	0.22	NS
Middle	37±2	40±3		
Older	30±2	37±3		
d/S1				
Young	0.25±0.01	0.18±0.02	<0.0001	NS
Middle	0.32±0.01	0.26±0.02		
Older	0.25±0.01	0.24±0.02		
S1/S2				
Young	1.98±0.08	2.08±0.11	0.013	NS
Middle	1.28±0.07	1.48±0.13		
Older	1.25±0.08	1.59±0.14		
D/I				
Young	1.42±0.04	1.57±0.05	0.015	NS
Middle	1.16±0.04	1.25±0.06		
Older	1.14±0.04	1.26±0.07		
RI				
Young	0.75±0.01	0.82±0.02	<0.0001	NS
Middle	0.68±0.01	0.74±0.02		
Older	0.75±0.01	0.76±0.02		
HR(bpm)				
Young	75±3	68±4	0.001	NS
Middle	80±2	63±4		
Older	73±3	68±5		

Data are means ± SE. Significance was set at p< 0.05. Legend: No significance (NS), resistance index (RI).

were as anticipated. HR was lower in exercise-trained than in sedentary (p=0.001). The S1 velocities were significantly higher in exercise-trained than in sedentary (p=0.001). The others (S2, D, d) had no significant differences for the exercise effect. Due to the significant increase in S1, it was reasonable that the indices of d/S1, RI and S1/S2 in the exercise-trained were significantly lower (p<0.0001), higher (p<0.0001) and higher (p=0.013), respectively. Interestingly, the index of D/I was also significant higher in the exercise-trained (p=0.015).

3.1.3 Differential effects of regular aerobic exercise

There were no differential training effects (training effect versus three age-groups) by ANOVA (p=NS) as shown in Table 4. The older, middle-aged and young groups had similar changes to the training. Fig. 3 represents the comparisons of the typical CCA blood flow velocity waveforms in three age-groups. There were no significant changes in the designed age-groups who regularly performed aerobic exercise training.

3.2 Protocol 2

In the intervention study, a decreased in the resting HR after a 1-month exercise training programme was a rough indication of the exercise effect From the 7 subjects selected in the study. The primary exercise for the subjects was road running for an average of 4.6±0.8 weeks, 3.2±0.5 times/week and 3.4±0.1 km/times. There were no significances in height, weight, BMI and BP after performing the exercise training (see Table 5).

Table 5: Selected subject characteristics of exercise intervention study

Variable	Before	After
n	7	----
Age (years)	23±1	----
Height (cm)	172±3	----
Weight (kg)	61±3	61±1
BMI (kg/m^2)	21±1	21±1
Systolic BP (mmHg)	114±4	109±3
Diastolic BP (mmHg)	64±2	67±5
Pulse BP (mmHg)	50±4	42±4
HR (bpm)	73±3	65±3*
RR (ms)	840±37	940±44*

All data are means ± SE. *p<0.05 versus before exercise training.

Regular aerobic exercise produced a decreased heart rate with the association of increased blood velocity waveforms in CCA. Table 6 show that exercise training improved blood flow velocities by 30 % (+4 cm/s training effect) for d velocity wave, by 11 % (+10 cm/s training effect) for S1 velocity wave, by 44 % (+12 cm/s training effect) for S2 velocity wave, by 42 % (+8 cm/s training effect) for I velocity wave, by 17 % (+7 cm/s training effect) for D velocity wave. Furthermore, there were significant increased in the ratio of d/S1 and decreased in the ratio of S1/S2 and D/I at the end of the physical training for 1 month.

As anticipated, this evidence of improvement in exercise was reinforced by a significant reduction of 11 % (-8 bpm training effect) in the resting HR and of 3 % in RI (-0.02 training effect), respectively.

Table 6: Exercise training enhanced blood velocity waveforms

Variable	before	after	p
d	12±1	16±2	0.02
S1	86±6	96±7	0.004
S2	27±3	39±3	<0.0001
I	19±2	27±2	0.0002
D	34±2	40±2	0.004
d/S1	0.15±0.02	0.18±0.02	0.05
S1/S2	3.44±0.44	2.57±0.27	0.004
D/I	1.84±0.19	1.51±0.16	0.006
RI	0.85±0.02	0.82±0.02	0.05

Data are means ± SE. Significance was set at p< 0.05.

4 DISCUSSIONS AND CONCLUSION

There were three major findings of this study. First, age-associated decrease in flow velocity waveforms in CCA (not only peak systolic S1 and end-diastolic minimum velocities d but also peak diastolic velocities D) was discussed. Second, regular aerobic exercise training could enhance age-associated reductions in blood flow velocity waveforms in young, middle and older age groups. Third, a relatively short-term (4-week) of regular aerobic exercise could restore some of the decrease of blood flow velocity in previously sedentary young men. The ability of regular aerobic exercise to increase blood flow velocities in this population does not depend on blood pressure. To our knowledge, there was a paper which demonstrated that the age-associated reduction in blood velocity waveforms of CCA could be modified favorably by regular aerobic exercise.

As to the age-associated decline in flow velocities found in this study, other groups had described a comparable decrease in flow velocities in the CCA [4-6, 22-25]. Most of their studies focused on blood flow velocity waveforms in CCA, i.e. on the S1 and d velocities, and demonstrated that the velocities decreased with age [4-6, 22-25]. Fujishiro *et al* measured blood velocity in the right common carotid artery in 140 normal healthy individuals in their teens to seventies using an ultrasonic quantitative flow measurement system [5]. As a result, they presented that S1 and d velocities markedly decreased with age, in which the values in the 70's were about 1/2 and 2/3 as small as that in the 20's, respectively [5]. Gregova *et al* suggested that S1 velocity in CCA significantly decreased during life, with the yearly rates of 7.39 mm/s/year [22]. These findings were consistent with age-related blood flow velocities decrease found in CCA. In our study, we found that not only S1 and d

velocities decreased continuously with age by 7.13 mm/s/year and 2.62 mm/s/year respectively but also, D velocity decreased by 1.22 mm/s/year.

In hemodynamics studies, characteristic blood flow velocities in S1, S2, and d were more focused on their relationship either between aging and carotid diseases [4-6, 22-25]. Our results suggest that not only S1, d velocities and its indices change with age, but also D velocities and its D/I index decreased continuously with age (r=-0.483, p<0.0001; r=-0.531, p<0.0001, respectively). Although the latter velocities and the ratio could be measured easily using ensemble-average envelope velocities, only very few studies took this parameters into considerations with the intention of characterizing its associations with disease [18,19], aging and exercise training.

Age-associated alterations in arterial properties comprised of structural, e.g. intima-media thickness (IMT), and functional, e.g. arterial elasticity, were related to changes of hemodynamic parameters particularly in peak blood flow velocity [23]. Age was the strongest predictor in the decrease of S1, which may be a suitable parameter to evaluate the influence of aging or atherosclerotic risk factor on arterial structure and function [23]. In the study, we also found that the decreases of D velocities and D/I index, which were depended on arterial elastic recoil, were the important determinant as predictor of age. The decrease may be homeostatically related to the reduction of arterial compliance and elasticity with age [1, 2, 23].

Yuhi classified blood flow velocity waveforms in CCA to 5 types according to the d/S1 as an index of blood flow and shape waveforms using ultrasonic Doppler sonography for assessing cerebrovascular disease [6]. He investigated the ratio of d/S1 in 15 healthy adults (aged 35-78 years), and suggested that the average ratio was 0.35 and it decreased with age. In our study, d/S1 index indicated was smaller in young group compared to that index in the middle-aged and the older group as shown in Table 3. However, there were similar results for the middle-aged to older age range that declined with age.

The ratio of S1/S2 known was altered with aging and ICA disease [7-9]. Gosling demonstrated that S1/S2 ratio in sonograms from the CCA decreased with aging [9]. Baskett et al. used the ratio for screening and diagnosis of carotid junction disease [8]. They suggested that when S1/S2 ratio was less than 1.05 there was an 88 % probability of disease at carotid junction [8]. In the study, S1/S2 ratio had similar results that significantly decreased with age (r=-0.578, p<0.0001) and markedly decreased in the sedentary middle-aged and older and also, this ratio seemed to have been improved in all groups by the training. It was expected that a decreased in the peak systolic velocity S1 was associated with increased second systolic velocity S2 with advancing age. The increased S2 may be related to the increased wave reflection properties caused by an increase in augmentation index and wasted ventricular energy.

Changes in the shape of velocity waveform may be quantified using RI as the most popular index. The index was originally used by Pourcelot on waveforms from CCA, as an indicator of peripheral vascular resistance beyond the measurement point [20, 21], where the smaller the RI the lower its resistance and vice versa. The index was dimension-less and independent of the angle insonation. It had been widely used for the study of pathophysiological conditions including internal carotid stenosis [21] and for the study of neotanal and fetal cerebral haemodynamics [26-27]. In the present study, RI had significant changes between the designed age-groups, but we could not confirm the relationship with age (r=-1.24, p=NS).

Second, one of most pronounced cardiovascular adaptation to aerobic exercise training was a lowered HR in the resting [28-30]. For instance, it had been reported that trained runners often possess resting HR lower than 50 bpm [30]. Similarly, lower resting HR had been shown to occur in sedentary individuals after they had been exposed to effective aerobic exercise training [31]. In our cross-sectional study, HR was lower in regular exercise trained subjetcs than in the sedentary peers. As anticipated, the resting HR decreased in previously sedentary young subjects after exercise intervention.

As shown in Fig. 3, there were typical blood velocity waveforms in three age-groups. Peak systolic velocities were seen to be extremely sharper and higher in the young group, exercise-trained middle-aged and older persons. All blood flow velocity waveforms were not significantly changed in subjects who regularly performed aerobic exercise training in the three age-groups. The velocities were sharper and higher than those of sedentary peers in the especially, elderly age. The adaptations of blood flow to regular exercise were similarly changed with aging (p=NS by ANOVA in Table 4). The patterns of blood flow waveforms were not significantly different between young, middle-aged and older exercise-trained.

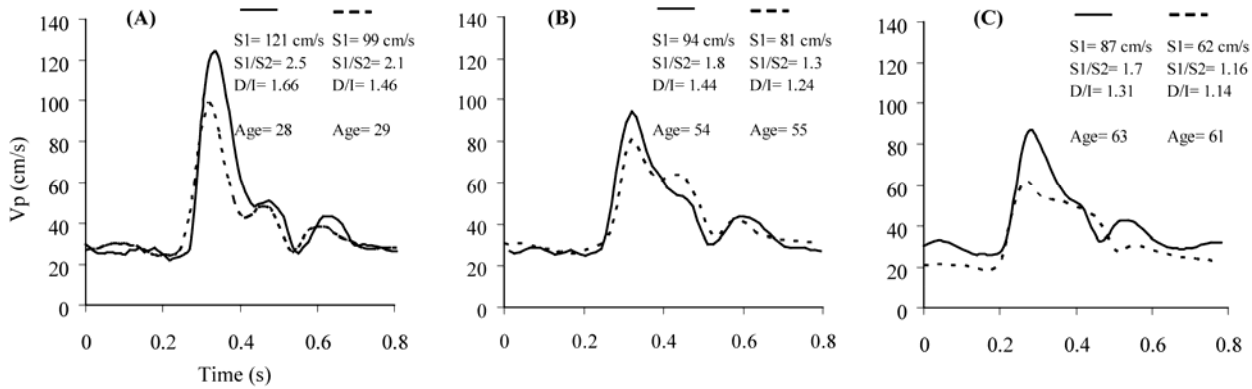

Figure 3: Comparisons of typical blood flow velocity waveforms for regular aerobic exercise-trained (solid line) and sedentary adults (dashed line) in young (A), middle-aged (B), and older (C) groups. Flow velocity waveforms between exercise-trained and sedentary individuals are markedly different in healthy middle and healthy older individuals. Regular exercise may retard age-associated diminishing in blood flow velocity waveforms in human.

S1 velocities had a significant difference between exercise-trained and sedentary adults. Due to the increased in S1 velocities, the indices of S1/S2, d/S1 and RI had a similar significant change with the training. Thus, training exercise was a predictor of increasing S1 velocities as a suitable parameter to evaluate the effect of training exercise. Another interesting finding to note was a higher D/I ratio in exercise-trained, despite absolute velocities of D and I, there were no significant differences between sedentary and exercise-trained. The decreased HR resting was associated with the increased S1 velocities and D/I ratio with training. We could only speculate on one of the adaptation of cardiovascular systems that regular aerobic exercise training improved arterial compliance and increased stroke volume in the present study. The increased S1 velocities seemed to reflect the changes of several structural and functional parameters including IMT and arterial compliance related to smooth muscle behavior in a similar way [23].

Finally, our intervention exercise study (protocol 2) allowed us to confirm these cross-sectional observations by demonstrating that regular aerobic exercise could increase blood flow waveforms in previously sedentary young subjects. We observed that all blood velocities increased after only 1-month of regular aerobic exercise in previously sedentary young men. The improvement associated with a decreased in the resting HR, may be related to enhancement of vagal activities [28-31]. However, exercise does not change blood pressure in young subjects [32]. These results suggested that relatively short-term aerobic exercise training could restore some of the diminishing blood flow in healthy adults. Furthermore, we observed that the effects of aerobic exercise on velocity waveforms, particularly in S1/S2 and D/I had different changes in young subjects.

Our findings had some potentially important clinical implications and requirements for prevention of cardiovascular disease in older persons. Reductions in blood flow velocities were believed to have contributed significantly to the pathophysiology of age-associated increase in not only cardiovascular but also cerebrovascular diseases.

There were some limitations. These data only supported the effect for regular aerobic exercise training but excluded the vigorous endurance exercise training, thus further studies were needed, particularly to determine dose-response relationship in middle and older age groups for exercise intervention study. Although, it was generally known that there were gender-linked differences in autonomic cardiovascular regulation, males and females were pooled because there was no gender effects for the selected study data. Further studies were also needed for the investigation of physiological blood flow, particularly for investigating cerebral blood flow regulations. The age-associated changes in blood flow volume were not mentioned in the study. Other previous studies suggested that blood flow velocity waveforms were highly correlated with total blood flow volume and mean blood flow velocity [4-6]. The Doppler angle of insonation was important because it must be taken into account when calculating blood flow velocity from the Doppler shift frequency. However, the waveform indices of S1/S2, d/S1, RI and D/I were independent of the insonating angle so that the assessments of hemodynamics were more reliable using these indices.

In conclusion, regular aerobic exercise training delays age-associated decrease in CCA blood flow velocities in the healthy middle-aged and older adults and partially restore the reductions of blood flow velocity in previously sedentary men. The blood flow waveform patterns have no markedly change with age in three age-groups who regularly performed aerobic exercise. Greater and sharper waveform patterns may contribute to the lower incidence of cardiovascular disease observed in middle-aged and older persons who exercise regularly.

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